REMARKS

Claims 13-36, 38, and 42-43 are now pending in the application, new claim 43 having been added by the above amendment. Support for new claim 43 can be found in claim 13 and in the specification, e.g., at page 3, lines 18-27. No new matter has been added.

Applicant thanks the Examiner and her supervisor for the courteous and helpful telephonic interview on June 15, 2005, with Applicant's representatives (Celia Leber and Janis Fraser) as well as Drs. Richard Summersell, Tomas Andersson, and Jan Trofast. The discussion of the pending rejections assisted Applicant in understanding the basis for the rejections, including why the rejection over Carling et al. that had been previously overcome was now reinstated and why the term "prevention" seemed to be an issue. This discussion helped Applicant formulate the response set forth below. In the course of the interview, Applicant's representative suggested possible alternative claim language to replace the term "prevention"; such alternative language is reflected in new claim 43. As indicated in the interview, Applicant prefers the term "prevention".

Rejections Under 35 U.S.C. §103(a)

Claims 13-15, 17, 18, 20-36, 38 and 42 have been rejected as unpatentable over Carling et al. Referring to Carling et al.'s teachings at page 6, lines 5-30, the Examiner takes the position that

> to instruct the patient to inhale, on demand, as determined by the patient's symptoms in acute asthmatic episode is obvious since Carling et al. teach that the dosages strongly depends on the severity of disease (mild, moderate, severe asthma) and the suitable daily dosage is up to 8 inhalation. One of ordinary skill in the art would be motivated to instruct those patient with severe asthma or acute asthmatic attack to use the Carling's composition as needed bases up to 8 inhalations as suggested by Carling et al. that the dosages strongly depends on the severity of disease and to achieve maximum benefit of daily dosage recommended by Carling et al....Moreover, if that patient experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, he still can safely inhale additional 6 inhalations without going over the maximum suitable daily dosage in general asthmatic condition taught by Carling et al. to achieve its known therapeutic relief from asthmatic attack. The skilled artisan would have been motivated to instruct the patient to use Carling's composition as needed bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any

severity condition of asthma in general including acute asthmatic condition. (Office Action, pages 7-8.)

Applicant maintains that the Examiner has misinterpreted this passage from Carling et al. Carling states that "The intended dose regimen is a twice daily administration" (Carling, page 6, third full paragraph). The varying dosage discussed by Carling in the remainder of that paragraph was meant to convey that different patients may be prescribed different daily doses that will depend on such factors as the particular patient's age and weight, and the severity of that particular patient's disease as determined by the physician. Any given patient is prescribed a fixed daily dose. Regardless of what fixed daily dose is prescribed for a given patient, that patient will be instructed to take the entire prescribed daily dose (no more and no less), split into just two administrations per day.

Once one understands how inhaled glucocorticosteroids such as budesonide were typically prescribed for asthma patients prior to Applicant's invention, it is apparent that Applicant's interpretation of Carling et al. is the one that a person of ordinary skill would have taken from Carling et al. To illustrate this, and to show that Applicant's present invention was in fact a paradigm shift in how glucocorticosteroids were prescribed for the treatment of asthma, Applicant submits a number of pieces of evidence marked as Exhibits A-E. For convenience, each section of an enclosed Exhibit that is discussed herein has been circled and labeled in the margin with a capital letter for ready reference.

In 1997 (the present application's priority date), budesonide was the active ingredient in an inhaler sold under the trademark Pulmicort® Turbuhaler® for maintenance treatment of asthma. A 1997 product insert packaged with the Pulmicort® Turbuhaler® is enclosed as Exhibit A. Recommended starting doses and highest recommended doses for various categories of patients are set out in a table in this document (Exhibit A, page 4, section A); each and every one of these doses is to be administered "twice daily." There is no provision for additional doses to be taken "as needed". Indeed, the section titled "Patient's Instructions for Use" on page 2 of the document repeatedly and emphatically instructs the patient not to take more or less than the exact dose prescribed by the physician, regardless of whether the patient is feeling better or

worse on a given day. The patient instructions concerning dosage (labeled as section B on page 2 of Exhibit A) are quoted in their entirety below for the Examiner's reference:

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler
- **DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER,** unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose. (Emphasis in original).

These instructions provide objective evidence that the paradigm for treatment of asthma with budesonide in 1997 was for a physician to prescribe a particular number of doses (generally two) per day for a patient and instruct the patient to take exactly that number of doses, no more or less. The third and last bullet points of the above instructions are particularly telling. Under no circumstances was the patient to take more doses than the specific number prescribed by the physician. Even if the patient missed a dose, the patient was not to take even a single extra dose. This is directly contrary to the Examiner's assertion that "one of ordinary skill in the art would instruct the patient with mild case of asthma with minimum dosage require to treat the diseases state and instruct to inhale on demand as needed is the symptoms persist up to the maximum daily limit taught by Carling et al." (Office Action, paragraph bridging pp. 11-12.)

Elsewhere the document says:

> Patients should take the medication as directed and use PULMICORT TURBUHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician....If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician. (Exhibit A, page 3, section C.)

This further illustrates that the physician, and not the patient, determines when the dosage of budesonide can be altered for a given patient. If the patient suffers an exacerbation of symptoms,

he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief: "PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma." (Exhibit A, page 2, section D.) "PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required." (Exhibit A, page 1, section E.) "If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur." (Exhibit A, page 3, section F.) "Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA [hypothalamic-pituitary-adrenal] dysfunction [a deleterious side-effect of glucocorticosteroid overdosing] may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose." (Exhibit A, page 3, section G.) These warnings make it clear that budesonide was understood to be useful for long-term prevention of asthma symptoms when used regularly in a fixed dose that is set (and carefully monitored) by the physician according to the patient's needs, but had no role in short-term relief of acute symptoms. The only medication that could be taken by the patient on an as-needed basis was a short-acting bronchodilator. The physician was explicitly directed to ensure that the patient received the lowest effective fixed dose of budesonide. Even in 1997 (four years after Carling), instructing the asthmatic patient to take additional doses of a budesonide composition on an as-needed basis was strictly forbidden. There was no evidence that taking budesonide more frequently than prescribed would be of any benefit to the patient, and there was a significant risk of harm.

That 1997 product insert pertained to budesonide itself, rather than a combination product. There are now at least two combination glucocorticoid/bronchodilator inhalation products (comparable to the combination product disclosed by Carling et al.) on the market for treatment of asthma. As elaborated below, for both products, the physician instructs the patient to inhale a set dose, twice per day--consistent with Applicant's (and not the Examiner's) interpretation of Carling et al.

One of these combination products is SYMBICORT TURBUHALER, a budesonide/formoterol inhalation powder product. Exhibit B is a product insert circa 2001 for that product. It says that the "recommended dosage" is 1-2 inhalations twice daily (Exhibit B, page 1, section A); when control of symptoms is achieved with the twice daily regimen, the physician can instruct the patient to reduce the number of inhalations to one daily (supra, section B). The insert instructs the physician to adjust the dosage to reflect the severity of the particular patient's disease. ("The dosage of the components of Symbicort Turbuhaler is individual and should be adjusted to the severity of the disease. This should be considered when treatment with combination products is initiated." Exhibit B, page 1, section C.) There is no suggestion anywhere in the document that the patient can be instructed to take it "as needed." To the contrary, use outside of the fixed dose is forbidden: "If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought." (Exhibit B, page 2, section D.) Moreover, "increasing use of rescue bronchodilators indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy"; "patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained." (Exhibit B, page 2, section E, and page 1, section F, respectively (emphasis added.) These instructions clearly indicate that if the patient experiences an increase or decrease in symptoms, the patient is to notify the physician so that the treatment protocol can be reassessed by the physician.

Likewise, the Advair Diskus® fluticasone propionate/salmeterol inhalation powder product is prescribed for use twice per day, at a dose set by the physician. The Patient's Instructions for Use (March 2003), attached as Exhibit C, emphasize repeatedly that the product

must be used neither more nor less often than instructed by the physician. The pertinent portion of these instructions, found on page 2 of the insert, is reproduced below:

2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**
3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder **that most, but not all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of medicine, you should not exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. If you are not sure you are receiving your dose of ADVAIR DISKUS, contact your doctor or pharmacist.
4. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or longer to achieve maximum benefit. It is **IMPORTANT THAT YOU USE ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.
6. **DO NOT USE ADVAIR DISKUS TO *RELIEVE* SUDDEN ASTHMA SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **An inhaled, short-acting bronchodilator such as albuterol should be used to *relieve* sudden asthma symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should continue to take ADVAIR DISKUS as instructed by your doctor.**

The patient is adamantly instructed not to use the product more frequently than 2 times daily, spaced approximately 12 hours apart, and to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms. Like the evidence discussed above, this evidence is directly contrary to the Examiner's assertions regarding what would have been "obvious" to one of ordinary skill in the art in view of Carling.

Clearly even as late as 2003 (long after the 1997 priority date of the present application), glucocorticoid-containing inhaled therapeutics were routinely prescribed solely for fixed-dosage use as maintenance therapy, and not for immediate relief of worsening symptoms. One of ordinary skill in the art of inhaled glucocorticoid therapy for treatment of asthma would have

understood in 1997 that patients were never instructed to take inhaled glucocorticoids on an "as needed basis". Carling et al. would certainly not have been read as recommending such a radical—and potentially dangerous—departure from the norm.

Further evidence concerning the proper interpretation of Carling is provided by the articles submitted herewith as Exhibits D and E. Exhibit D is a journal article (O'Byrne et al., "Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma", Am J Respir Crit Care Med 171:129-136, 2005) discussing the positive results of a recent clinical trial studying the efficacy of the claimed method in providing rapid symptom relief and simultaneous adjustment in anti-inflammatory therapy, thereby reducing the incidence of exacerbations. Exhibit E (Barnes, "A Single Inhaler for Asthma?", Am J Respir Crit Care Med 171:95-96, 2005) is an editorial, in the same journal issue, by an eminent researcher in the asthma field. Dr. Barnes states his opinion that "the study by O'Byrne and his colleagues may lead to changes in *the paradigm of asthma management.*" (Exhibit E, page 95, last paragraph, emphasis added.) Moreover, Dr. Barnes views the success of Applicant's treatment protocol as "remarkable":

> The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. (page 95, col.1, last paragraph)

Dr. Barnes explains in the carryover sentence of col.1-2 one reason why this approach was not previously contemplated: "A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid." He then notes that this turned out not to be a problem in practice. In fact, the patients instructed to take the budesonide/formoterol combination on an as-needed basis inhaled on average only one additional dose per day, yet this approach was more effective in preventing exacerbations than doubling the fixed daily amount of budesonide had proven in a different study. Dr. Barnes notes that these are "surprisingly good results." (page 95, col.2, first full paragraph)

It is to be kept in mind that these statements by Dr. Barnes, including the characterization of the O'Byrne et al. report as "surprisingly good results", were made this year, 12 years after the Carling reference was published. In the heavily researched field of asthma treatment, if Applicant's invention had indeed been obvious from Carling's teachings, Applicant's treatment protocol would not now be regarded as a radical departure from the norm.

It is clear from the above evidence that one of ordinary skill in the art of asthma therapy in 1997 would not have interpreted Carling et al. as teaching that patients should be instructed to inhale a budesonide-containing product on an as-needed basis. The paradigm for use of budesonide-containing products dictated fixed dosage use for maintenance therapy, not variable dosage for relief of an acute attack. Consistent with that paradigm, Carling et al. was simply saying that the physician can set the fixed dosage within certain parameters, based on the age, weight and condition of the patient. Certainly Carling et al. gave no reason to expect the "surprisingly good results" reported by O'Byrne et al. Withdrawal of the rejection over Carling et al. is respectfully requested.

Claims 16 and 19 have been rejected as being unpatentable over Carling et al. in view of Aberg and Ryrfeldt. These claims are patentable for at least the reasons discussed above, as Aberg and Ryrfeldt do not remedy the deficiencies of the Carling reference.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 13, 35, 36 and 42 were rejected under 35 USC §112, first paragraph. The Examiner acknowledges that the specification is enabling for the "treatment of an acute episode of asthma," but alleges that the specification does not reasonably provide enablement for the "prevention of an acute episode of asthma." (Office action, page 2) The Office action explains that the state of the art of "preventing" acute episodes is "underdeveloped", and that the specification does not provide sufficient guidance in how to do so. According to the Office action, actual "prevention" of an acute episode of asthma, a complex disorder with potentially many different causes, would therefore be unpredictable and require undue experimentation. Applicants traverse.

First, Applicant notes that, contrary to the Examiner's position, the specification provides ample guidance in how to prevent an acute episode of asthma. It is really quite simple. According to the specification at page 3, lines 18-19, "We contemplate preventive use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions." The patient will know ahead of time when at least some of these asthma-inducing conditions are about to be encountered, and so will know when to take the preventative dose of the claimed composition. As the formoterol part of the composition is formulated to prevent bronchoconstriction, Applicant predicted that taking it shortly before encountering the asthma-inducing conditions would prevent the acute episode that otherwise is likely to take place. And the slower-acting budesonide that is inhaled at the same time as the formoterol acts to prevent inflammation over the long term, thereby preventing future acute exacerbations by reducing the underlying inflammation aspect.

Given the clear and irrefutable logic of the above, it appears that the actual basis for this rejection may be more a concern that the term "prevent" is simply too strong of a word to be applied in the context of asthma. If this is indeed the concern, Applicant asks the Examiner to use a realistic, art-recognized definition of the word "prevent". It does not mean that the patient has to be cured of his asthma. Anti-inflammatory agents such as budesonide have long been used as "maintenance" drugs to control symptoms and reduce the number of exacerbations experienced by the patient, regardless of the underlying triggering cause. When such agents work this way, they are commonly said to "prevent" the symptoms or the exacerbations (i.e., acute episodes). See, for example, the "Patient's Instructions for Use" section on page 2 of the PULMICORT TURBUHALER budesonide inhalation powder inhaler product insert attached as Exhibit A (dated June 1997). This section tells the patient that "Pulmicort Turbuhaler works to prevent and reduce your asthma symptoms and attacks." (Exhibit A, page 2, section H; emphasis added)

See also the various internet publications printed out by Applicant's representative on June 23, 2005, and enclosed as Exhibit F (only the first page of each publication is provided, as the relevant language appears there). Each of these publications uses the term "prevent" in a

manner that is consistent with Applicant's position (see circled text on each page). The first describes budesonide as a drug "used to prevent asthma attacks". The second says that "Regular use of budesonide inhalation powder will help prevent asthma attacks." The third says "Budesonide inhalation will not stop an asthma attack that has already started. It is used to prevent attacks." These were a few of the first ones found by a simple GOOGLE search for internet sites with the terms "prevent", "asthma" and "budesonide" (27,800 hits found in 0.1 sec). When the search was broadened to simply "prevent" and "asthma", there were over 2 million hits. Applicant will spare the Examiner the burden of reviewing all 2 million (or even all 27,800) publications, but does want to be certain the Examiner is aware that acute episodes of asthma can indeed be "prevented" with appropriate use of asthma drugs. That this was true, and was recognized in the art, back at the time the present application was filed is established by the evidence in Exhibit A. There is therefore no rational basis for taking the position that those in the art would have believed "prevention" of an acute episode of asthma is *a priori* unpredictable or would require undue experimentation.

Finally, Applicant points out that the O'Byrne et al. publication submitted as Exhibit D and discussed above illustrates that the presently claimed method of instructing the patient to inhale a budesonide/formoterol composition on an "as needed" basis does indeed result in a decrease in the number of acute episodes of asthma experienced by the patient. That could happen only if some of those acute episodes were "prevented".

Withdrawal of the rejection is therefore requested.

Applicant notes that new claim 43 does not use the word "prevention" or "preventive", but rather is drawn to a method of "reducing the incidence of acute asthma attacks." Allowance of claim 43, in addition to the previously presented claims, is respectfully requested.

Enclosed is a $200 check for excess claim fees. Apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 06275-188001.

Respectfully submitted,

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